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PII: S0012-1606(17)30458-X  
DOI: <https://doi.org/10.1016/j.ydbio.2017.12.013>  
Reference: YDBIO7651

To appear in: *Developmental Biology*

Received date: 30 June 2017  
Revised date: 5 December 2017  
Accepted date: 18 December 2017

Cite this article as: Jialiang S. Wang, Carlos R. Infante, Sungdae Park and Douglas B. Menke, PITX1 Promotes Chondrogenesis and Myogenesis in Mouse Hindlimbs Through Conserved Regulatory Targets, *Developmental Biology*, <https://doi.org/10.1016/j.ydbio.2017.12.013>

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# PITX1 Promotes Chondrogenesis and Myogenesis in Mouse Hindlimbs Through Conserved Regulatory Targets

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## ABSTRACT

The PITX1 transcription factor is expressed during hindlimb development, where it plays a critical role in directing hindlimb growth and the specification of hindlimb morphology. While it is known that PITX1 regulates hindlimb formation, in part, through activation of the *Tbx4* gene, other transcriptional targets remain to be elucidated. We have used a combination of ChIP-seq and RNA-seq to investigate enhancer regions and target genes that are directly regulated by PITX1 in embryonic mouse hindlimbs. In addition, we have analyzed PITX1 binding sites in hindlimbs of *Anolis* lizards to identify ancient PITX1 regulatory targets. We find that PITX1-bound regions in both mouse and *Anolis* hindlimbs are strongly associated with genes implicated in limb and skeletal system development. Gene expression analyses reveal a large number of misexpressed genes in the hindlimbs of *Pitx1*<sup>-/-</sup> mouse embryos. By intersecting misexpressed genes with genes that have neighboring mouse PITX1 binding sites, we identified 440 candidate targets of PITX1. Of these candidates, 68 exhibit ultra-conserved PITX1 binding events that are shared between mouse and *Anolis* hindlimbs. Among the ancient targets of PITX1 are important regulators of cartilage and skeletal muscle development, including *Sox9* and *Six1*. Our data suggest that PITX1 promotes chondrogenesis and myogenesis in the hindlimb by direct regulation of several key members of the cartilage and muscle transcriptional networks.

*Keywords:*

PITX1, Hindlimb, *Anolis*, Mouse, Chondrogenesis, Myogenesis

## 1. Introduction

The *Pitx1* gene encodes a bicoid-class homeodomain transcription factor that plays a central role in growth and patterning of the vertebrate hindlimb (Lanctôt et al., 1999; Szeto et al., 1999). The complete ablation of *Pitx1* function in mice results in reduced

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