

New insights into limb formation

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Investigators at Burnham Institute for Medical Research (Burnham) and the University of Connecticut Health Center (U.C.H.C.) have gained new understanding of the role hyaluronic acid (HA) plays in skeletal growth, chondrocyte maturation and joint formation in developing limbs. Significantly, these discoveries were made using a novel mouse model in which the production of HA is blocked in a tissue-specific manner.

The Yamaguchi laboratory genetically modified the Has2 gene, which is a critical [enzyme](#) for HA synthesis, so that the gene can be "conditionally" disrupted in mice. This is the first time a conditional Has2 knockout mouse has been created, a breakthrough that opens vast possibilities for future research. The paper was published online in the journal *Development* on July 24.

HA is a large [sugar molecule](#) that is produced by every cell in the body and has been thought to play a role in joint disease, heart disease and invasive cancers. Yu Yamaguchi, M.D., Ph.D., a professor in the Sanford Children's Health Research Center at Burnham and Robert Koshier, Ph.D., a professor in the Center for Regenerative Medicine and Skeletal Development at U.C.H.C. and colleagues showed that [transgenic mice](#), in which Has2 was inactivated in the [limb](#) bud mesoderm, had shortened limbs, abnormal growth plates and duplicated bones in the fingers and toes.

"Because hyaluronic acid is so prevalent in the body, it has been difficult to study," said Dr. Yamaguchi. "Systemic Has2 knockout mice died mid-gestation and could not be used to study the role of HA in adults. By

inactivating Has2 in specific tissues, we give ourselves the opportunity to study the many roles HA plays in biology. This mouse model will be useful to study the role of HA in various age-related diseases and conditions, such as arthritis and skin aging, as well as cancer."

To create the conditional knockout mice, the Yamaguchi laboratory genetically engineered the Has2 gene to create the Has2flox allele. The team then added the Prx11-Cre transgene, which is associated with early limb bud mesenchyme to produce the conditional Has2 knockout mice.

Source: Burnham Institute ([news](#) : [web](#))

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