UNIVERSITÉ DE GENÈVE

PRESS RELEASE

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The origin of our digits

Scientists from UNIGE, EPFL, and the Collège de France show that a regulatory region of the genome, initially dedicated to the formation of the fish cloaca, has been co-opted by evolution to guide the development of digits.

To develop their digits, ancestral tetrapods recycled an ancient region of the genome that was initially active in the formation of the fish cloaca. This is illustrated here by the expression of a Hox architect gene in the cloaca of the zebrafish (black dot).

High resolution pictures

How did digits evolve? While it is clear that they derive from genetic programs already present in fish, their precise origin remained a matter of debate. An international team led by the University of Geneva (UNIGE) with EPFL, the Collège de France, and the universities of Harvard and Chicago has come up with an unexpected answer: digits may have evolved from the reuse of an ancient region of the genome, initially active in the formation of the fish cloaca rather than their fins. Published in *Nature*, this discovery reveals a major evolutionary strategy that consists of recycling what already exists rather than building something new.

380 million years ago, our fish ancestors began to colonise dry land, evolving into numerous vertebrate species equipped with, among other things, lungs capable of absorbing oxygen, as well as feet and hands. Understanding how these limbs appeared remains one of the oldest and most debated scientific questions. Did they evolve from fins, the homologues of our arms and legs, or, conversely, are they entirely new structures?

Change of perspective

To answer this question, the research team did not just study the genes involved in the development of the digits themselves, but also explored the vast non-coding regions of the genome (the set of chromosomes and genes of a species or individual) that control their expression and activation. These regions are called “regulatory landscapes” and are much larger than the coding regions, which make up only 2% of the genome, they act as veritable “control towers” for gene expression.

By comparing the genomes of mice and fish, the researchers first identified a regulatory landscape conserved between the two species and involved in the development of mouse digits. Then, by removing this large region of DNA in fish using CRISPR/Cas9 technology – genetic scissors that enable genome editing – the team observed a loss of gene expression in the cloaca, but not in the fins.

This surprising result suggests that the cloaca – an organ where the intestinal, excretory, and reproductive systems meet at their extremities in many species – has been reused in terrestrial vertebrates to develop digits. “The common feature between the cloaca and the digits is that they represent terminal parts. Sometimes they are the end of tubes in the digestive system, sometimes the end of feet and hands, i.e. digits. Therefore, both mark the end of something," says Aurélie Hintermann, a former doctoral student at UNIGE, now a postdoctoral fellow at the Stowers Institute (USA) and co-author of the study conducted as part of her PhD thesis.

Evolutionary recycling

In particular, the regulatory landscapes in question control the activation of Hox genes, known as "architect genes." They establish the body's organisational plan by determining the position and identity of segments or organs. They act at the top of a complex network of thousands of operational genes by controlling their expression. A mutation in these genes can therefore lead to profound anatomical changes, which certainly explains their decisive role in evolution.

"The fact that these genes are involved is a striking example of how evolution innovates, recycling the old to make the new," comments Denis Duboule, honorary professor at UNIGE and the Collège de France and initiator of the study. "Rather than building a new regulatory system for the digits, nature has repurposed an existing mechanism, initially active in the cloaca."

A new piece in the puzzle of evolution

It is therefore not only the operational or coding genes that evolve, but above all the architecture of their regulation. And sometimes, an entire region can be recycled in another morphological context, as is the case with the cloaca and digits. The question now is not where these changes appear in the genome, but how, in order to continue describing the mechanisms of evolution and explain the transition from a distant aquatic ancestor to today's fish and humans.

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