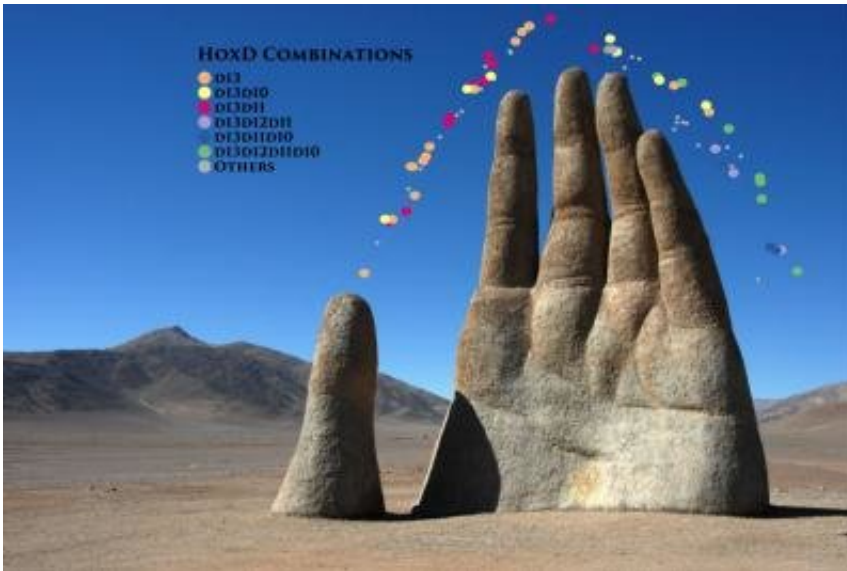


The gene code of growing limbs

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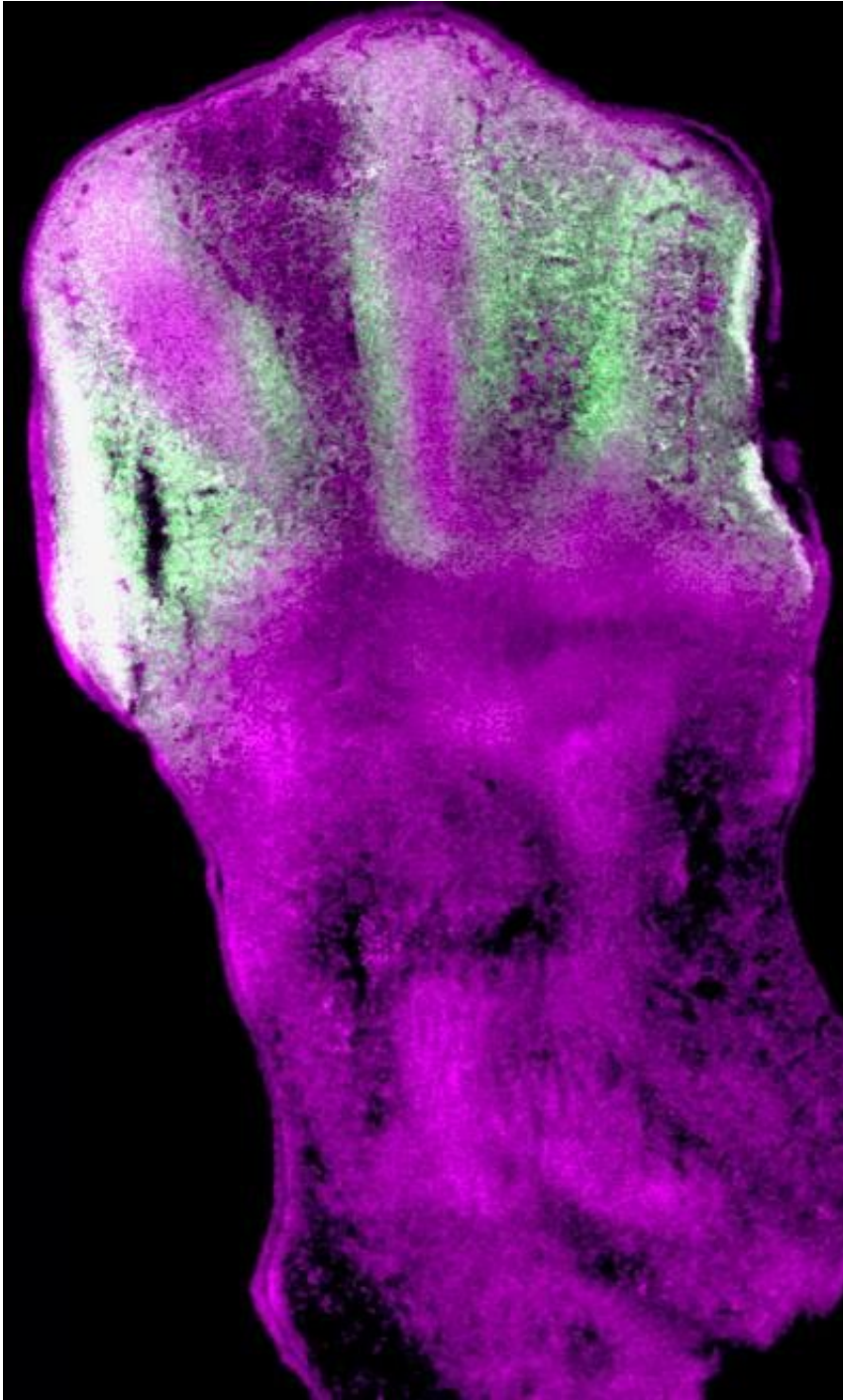
The image below is an overlay of the large-scale hand sculpture with Hox genes combinatorial code distribution along a diffusion map, illustrating genetic diversity in the growing limb. Each dot being one cell, the colors represent the single-cell combinatorial Hoxd code that match with different degree of differentiation, a recent concept also described as pseudo-temporal ordering of single-cells. The graphic highlights the switch between cellular temporal states involved in a regulatory network. The cells with only one gene are in a more premature state while the one expressing a higher set of these genes being at the end of their maturation. Credit: Sculpture 'and del desierto' from Chilean sculptor Mario Irrarazabal in Atacama desert. Graphical representation of pseudotime by P. Fabre and Q. Lo Giudice, University of Geneva.

When a fetus develops, cell division and differentiation, gene

expression, cell-to-cell signaling, and morphogenesis must be carefully coordinated to occur in the correct sequence and for the proper amount of time. Failures in timing can result in congenital deformities, disabilities, and even death. For a long time, developmental biologists have sought to determine what sets the pace and directs the order of developmental events.

Studying the development of the paw and digits in mice, scientists from the lab of Denis Duboule at EPFL, with Pierre Fabre at the University of Geneva, have now discovered a "code" of architect [genes](#) that play a central role in the developmental cascade. The genes belong to the Hoxd group, [developmental genes](#) that are active in various combinations inside so-called "progenitor" cells, which are just a step more specialized than stem cells.

By pushing a cutting-edge single-cell RNA sequencing technique to its maximal resolution, the scientists were able to study the expression patterns of thousands of genes inside single [progenitor cells](#). The analysis showed that each cell contains 343 genes that are associated with specific cellular states, many of which are involved in the packaging and ordering of DNA in the cell, as well as patterning how the paw's fingers will develop.



The reconstructed 20X image above (from 54 adjacent photos) represents a section through a developing mouse embryonic arm and hand. All cells are stained in magenta superimposed with a green signal in the cells expressing the mRNA of Hoxd13 gene, one of the five architect gene participating in the formation of the fingers. Credit: Pierre Fabre and Jessica Dessimoz, EPFL

The scientists identified a very restricted set of six main combinations of five Hoxd genes (Hoxd9, 10, 11, 12 and 13) in the development of digits in mice. Each combination includes one, two or four of the genes, with the simplest (one gene) at the beginning of development and the more complex combination (four genes) occurring at the later stages of maturation.

The pattern by which Hox genes are expressed when they "build" the entire body—in both mice and humans—has been known and studied for over 30 years. But most of that information comes from looking at entire tissues of developing organs. In contrast, this study is the first to look at it in single cells, offering a higher resolution and clarity in the way Hox genes orchestrate the rhythm of development.

"The study shows how [architect genes](#) act in concert, following a gradual progression in every developing cell to generate our fully mature arms and hands at the right time and the right place," says Pierre Fabre. "The Hoxd gene combinations provide a machinery that generate a spectrum of functionally different cells within genetically defined classes of limb patterning motifs. This will pave the way for future genetic work to understand how [cells](#) get to synchronize the combined activation of multiple genes."

More information: P. J. Fabre et al, Heterogeneous combinatorial expression of Hoxd genes in single cells during limb development, *BMC Biology* (2018). [DOI: 10.1186/s12915-018-0570-z](https://doi.org/10.1186/s12915-018-0570-z)

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