

Evolution: The genetic connivances of digits and genitals

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During the development of mammals, the growth and organization of digits are orchestrated by Hox genes, which are activated very early in precise regions of the embryo. These "architect genes" are themselves regulated by a large piece of adjacent DNA. A study led by Denis Duboule, professor at the University of Geneva (UNIGE) and the Federal Institute of Technology in Lausanne (EPFL), Switzerland, reveals that this same DNA regulatory sequence also controls the architect genes during the development of the external genitals.

The results published in *Science* magazine, indicate that a unique ancestral regulatory structure existed, which evolved into a digit-specific or genital-specific control mechanism, by implementing very small modifications into the general process.

During our embryonic development, the emergence and organization of the body structures are orchestrated by a family of "architect genes" called Hox, each providing precise instructions at a given time. The team of Denis Duboule, a geneticist at the UNIGE and the EPFL, had already shown that the Hox genes responsible for the formation of digits were themselves controlled by specific DNA sequences located in an adjacent region. These numerous regulatory sequences act as molecular switches, activating or inhibiting the expression of the genes targeted.

Small differences with a decisive impact

Certain Hox genes are endowed with the ability to organize the construction plan of the body at different scales: once the anteroposterior axis is established, the same genes are recruited again for the development of the digits and of the external genitals. "We wanted to determine how the regulation of identical Hox genes expressed in such different contexts is achieved", says Nicolas Lonfat, PhD student at the Laboratory of Developmental Genomics of the EPFL and researcher involved in these results.

At the UNIGE and the EPFL, researchers from Denis Duboule's two laboratories have then collaborated to answer this question. By using namely a cutting-edge technique called "chromosome conformation capture" on mouse embryos, they were able to demonstrate that the same regulatory DNA sequence controls architect genes for growth of the external genitals and the digits. "Identical ancestral mechanisms are implemented, explains Denis Duboule. They lead to the formation of the penis or the clitoris, or to the production of digits, depending on small differences in the use of the DNA regulatory sequences." These results illustrate the parsimony of evolutionary mechanisms, which always tend to reuse something that works well.

Digits or genitalia, which came first?

Of the digits or the external genitalia, which were likely to precede the other during evolution? These results indeed suggest that one structure evolved based on the existence of the other by hijacking the genetic processes at work. "It is however difficult to determine which appeared first, since both digits and genitals were likely of great adaptive values at the time of the transition from an aquatic to the terrestrial environment", comments Nicolas Lonfat. Indeed, digits were undoubtedly essential for the locomotion, and external genitals for an efficient type of internal fertilization.

The common use of the same genes and regulations for both types of body structures may explain why some genetic syndromes in human are associated with concomitant malformations in both the penis, such as hypospadias, and hands and feet, such as polydactyly or brachydactyly.

More information: "Convergent evolution of complex regulatory landscapes and pleiotropy at Hox loci" *Science* ,
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