



PRESS RELEASE

Geneva | 4 June 2013

embargoed until June 6th, 2pm US Eastern Time

THE SWING OF ARCHITECT GENES

A study led by Denis Duboule shows that the genes that preside over limb formation successively come into contact with different regulatory domains. This sequential swing enables modular limb construction, with articulations as an added bonus.

Architect genes are responsible for organizing structures of the body during embryonic development. Some of them, namely the *Hoxd* genes, are involved in the formation of forelimbs. They are activated in two successive waves, enabling the formation of the arm, then the hand. A team led by Denis Duboule, a professor at UNIGE and EPFL, Switzerland, and Guillaume Andrey, from the *Frontiers in Genetics* National Research Center, uncovered the workings of this complex process and published their findings in *Science*. The researchers describe how various *Hoxd* genes successively interact with two adjacent regulatory domains, leading to the development of the arm and hand, respectively. As for wrist formation, it originates from a region at the interface of these two regulatory spheres, in which the *Hoxd* genes are inactive.

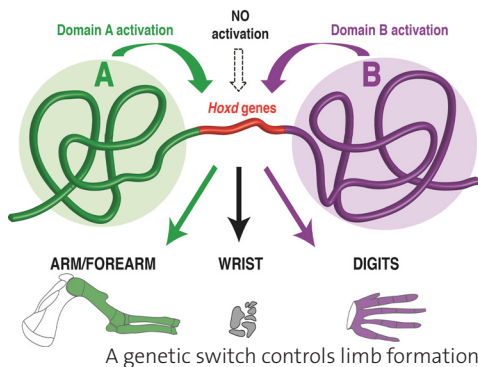
A few days. This is the short period of time during which our body's construction plan is put in place, during its embryonic life. The appearance of limbs and vertebrae is orchestrated by a family of 'architect' genes called *Hox*, each providing precise instructions at a given time. Denis Duboule, a geneticist at the Faculty of Science of the University of Geneva (UNIGE) and at the Swiss Federal Institute of Technology in Lausanne (EPFL), demonstrated that these genes were aligned within our chromosomes according to the order of structures that will emerge: first the components of the shoulder, then the arm, and finally the fingers.

The cluster of *Hoxd* genes coordinates the operations of limb formation, in particular. These genes are transcribed in two successive waves, allowing the development of the arm, then the hand. 'We had already discovered that the genes responsible for the hand were controlled by enhancers, specific DNA sequences located in an adjacent area, at one end of the *Hoxd* cluster. This regulatory domain takes on a different three-dimensional configuration, according to the degree of activity of the enhancers,' says Professor Duboule.

Two distinct regulatory domains

In order to understand the molecular processes that preside over arm formation, as well as the transition to wrist and hand formation, the researchers used sophisticated techniques of genetic engineering, molecular biology, and murine embryo cell lines. 'Curiously, certain *Hoxd* genes are involved in the origin of both the arm and the hand, while it is their absence of expression that enables wrist formation', notes Guillaume Andrey, former doctoral student at the *Frontiers in Genetics* National Research Center and first author of the article.

The biologists demonstrated the existence of a second regulatory do-



© Diagram: Guillaume Andrey



main. However, it is responsible for arm development and is located at the other end of the *Hoxd* gene cluster. They decrypted the complex dialogue established between these genes and the two adjacent domains: 'certain *Hoxd* genes associate with only one of the two domains, whereas others interact with both, but in different cells and at separate times,' explains Guillaume Andrey.

The wrist emerges from a no man's land

During the growth of the limb bud, certain *Hoxd* genes will shift toward the opposite regulatory domain to establish new contacts. This swing from one domain to the other is the equivalent of a genetic switch, signaling the transition between the creation of the arm and the hand. However, there is an intermediary cellular territory that escapes the two regulatory controls and in which the switch is not activated: this zone will generate the wrist. Thus, the articulation of activities between domains A and B enables the appearance of a morphological articulation between our arms and our hands.

'The three-dimensional organization of these two regulatory domains, which gives them physical and functional independence, plays an essential role in stimulating the *Hoxd* genes. These experiments allowed us to demonstrate that there is an additional, topological level of information to modulate gene expression. This is a first!' says Guillaume Andrey.

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contact

Denis Duboule

+41 22 379 67 71
denis.duboule@unige.ch

Guillaume Andrey

+41 21 693 97 04
guillaume.andrey@epfl.ch

UNIVERSITÉ DE GENÈVE **Service de communication**

24 rue du Général-Dufour
CH-1211 Genève 4

Tél. 022 379 77 17
media@unige.ch
www.unige.ch