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Finger (mal)formation reveals surprise function of desert DNA

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Swiss scientists from the EPFL and the University of Geneva have discovered a genetic mechanism that defines the shape of our members in which, surprisingly, genes play only a secondary role.

The research published in *Cell*, online the 23rd of November, shows the mechanism is found in a DNA sequence that was thought, incorrectly, to play no role. This long string has seven enhancers which, when combined with one another, modulate the activity of the genes responsible for the formation of the fingers – an important fundamental discovery for the field of genetics. The discovery could notably help better understand anomalies that are transmitted from generation to generation such as welded fingers or extra or abnormally short fingers (Kantaputra syndrome) even if the genes appear perfectly normal.

Turbos on the genome

DNA is composed of only about 2% genes. But it has other types of sequences, such as enhancers that increase the activity of certain genes at key moments. "The discovery we have made is that the group of genes involved in finger growth is modulated by seven enhancers, not just one, and they combine through contact," says Thomas Montavon, lead author of the article and researcher at the EPFL.

When the fingers in the embryo begin to take shape, the string of DNA folds and the enhancers, located on different parts of the string, come

into contact. They then bring together various proteins that stimulate the activity of the genes, and the fingers start to grow. If one of these seven enhancers is missing, the fingers will be shorter, or abnormally shaped. When two are missing, the defects are even more pronounced. Without enhancers, the genes work slowly, and generate only the beginnings of fingers.

How does the DNA fold in exactly the right way so that the enhancers will correctly do their job? The recently discovered process remains largely unexplained. "In other tissues, such as the brain, the string of DNA folds differently," says Denis Duboule, director of the study and researcher at both the EPFL and the University of Geneva. "To our knowledge, it is only in the fingers that it adopts this shape."

An explanation for evolutionary diversity

Statistically, the seven enhancers involved in finger growth create seven opportunities for a mutation to occur. The flexibility of this mechanism, with no known equivalent to date, causes not only hereditary malformations, but also the many variations in the hands, legs and other appendages in nature. "Just think of some ungulates, which walk on a single finger, or the ostrich, which has only two, and the human hand, of course" explains Denis Duboule.

Other genetic processes may also function on the basis of a similar principle. This could explain the diversity of the products of evolution, in areas other than the fingers, according to Denis Duboule. "When a mutation occurs on a gene, for instance in cystic fibrosis, it is often binary. This amounts to an 'all or nothing' situation. With the mechanism we have discovered, it is a 'more or less' situation. It is combined, it is modulated."